



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Patent Application of Hiroyuki ODAKA et al.

Serial No. 09/380,059

Group Art Unit: 1614

Filed: August 25, 1999

Examiner: James D. Anderson

For: PHARMACEUTICAL COMPOSITION

**DECLARATION UNDER 37 C.F.R. §1.132**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

1. I, Hiroyuki ODAKA, a citizen of Japan, residing at 12-12, Katsuragi 2-chrome, Kita-ku, Kobe, HYOGO, Japan, declare that:

2. I was born on December 9, 1955, in Hiroshima, Japan;

3. I graduated with a bachelor degree from the Department of Agriculture, Tohoku University, Japan, on March 1977;

4. I was awarded an Agricultural doctoral degree from Tohoku University, Japan, on February 1991, on a doctoral thesis entitled "study on environmental factors affecting on the development of noninsulin-dependent diabetes mellitus";

5. I have been an employee of Takeda Chemical Industries, Ltd., Osaka Japan since April, 1979;

6. I am not being compensated for submitting this declaration beyond my salary as an employee of Takeda;

7. I have been engaged in research work in the field of pharmacology and physiology on diabetes mellitus and hyperlipidemia;

8. I am a Director of Pharmacology Research Laboratories 1, Pharmaceutical Research Division of said company;

9. I am a member of the Japanese Diabetes Society;

10. I am a co-inventor of the invention claimed in U.S. Patent Application Serial No. 09/380,059;

11. I am submitting this declaration in order to provide (1) a statistical analysis (more specifically, Tukey Tests) on the Experimental data in the Declaration previously filed on March 07, 2003, (2) corrections of clerical errors in the Declaration previously filed on March 07, 2003, and (3) confirmation that these experiments were carried out by myself or technicians under my direct guidance and supervision.

**Statistic Analysis of the HbA1 c% Data**

Table 3. Tukey Tests on HbA1 c% of Groups A, B, C, and D

Comparison between	Group A & Group B	Group A & Group C	Group B & Group C	Group A & Group D	Group B & Group D	Group C & Group D
p-Value	0.6155	0.8572	0.9665	<0.01	<0.05	<0.01
95% confidence	<i>Not</i> significant	<i>Not</i> significant	<i>Not</i> significant	significant	significant	significant

12. As shown in Table 3, no significant difference was observed between Group B (using only pioglitazone) and Group A (control), Group C (using only sibutramine) and Group A (control), and also between Group B and Group C. However, the result of Group D (using a combination of pioglitazone and sibutramine) differ from Groups A, B, and C significantly, showing an unexpected synergistic effect of using the combination of pioglitazone and sibutramine.

**Correction of Clerical Errors in the Declaration filed on March 07, 2003**

13. On March 26th, 2008, I discovered minor errors in Tables 1 and 2 in the Declaration filed on March 07, 2003 that were brought to my attention by my subordinate. He discovered these minor errors after he reviewed the Office Action questioning the

statistical significance of the results in my 2003 Declaration, which caused him to go back and review the numbers.

14. More specifically, the minor errors in Tables 1 and 2 are shown in the following tables (if there is no statement that a change is made then the previous value is the correct value):

Table 1

	HbA1c (%)	Plasma glucose (mg/dl)	Plasma triglyceride (mg/dl)
Group A(Control)	$0.1 \pm 0.5$	$37.8 \pm 75.5$	$164.7 \pm 52.2$
Group B(pio)	$- 0.3 \pm 0.3$	Previously gave incorrect value as $- 0.3 \pm 60.7$ ; the correct value is $- 0.4 \pm 60.7$	$78.7 \pm 102.9$
Group C(sib)	$- 0.2 \pm 0.5$	$- 83.2 \pm 48.3$	$- 36.2 \pm 94.3$
Group D(pio+sib)	$- 1.2 \pm 0.4$	$- 101.4 \pm 55.2$	$- 67.3 \pm 106.9$

Mean  $\pm$  SD

Table 2

	Body weight increase (g)
Group A(Control)	Previously gave $85.4 \pm 10.8$ , but the correct value is $85.4 \pm 10.6$
Group B(pio)	Previously gave $108.4 \pm 14.8$ , but the correct value is $106.4 \pm 14.8$
Group C(sib)	Previously gave $82.0 \pm 16.8$ , but the correct value is $62.0 \pm 16.8$
Group D(pio+sib)	Previously gave $70.8 \pm 8.3$ , but the correct value is $70.6 \pm 8.3$

Mean  $\pm$  SD

15. Also, on page 2, line 6 of the Declaration filed on March 07, 2003, I incorrectly indicated that Group B had 5 rats, but it actually had 6 rats.

16. The above errors occurred for the following reasons:

In Table 1, I incorrectly took “-0.3” as the half adjust of “- 0.35” (raw average of Plasma glucose concentration (mg/dl) observed in Group B). It is now corrected by replacing “-0.3  $\pm$  60.7” with “-0.4  $\pm$  60.7”.

In Table 2, I incorrectly recorded some of letters "8" as "6" in the previous filed declaration, due to the small font size in the lab notes.

On page 2, line 6 of the Declaration filed on March 07, 2003, there was a typographical error that caused the mis-statement in the number of rats used.

17. I further believe that all of these errors are minor errors that do not alter my conclusions in the prior Declaration or in this Declaration.

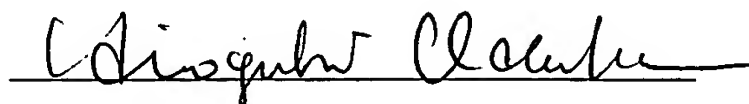
18. The statistical analysis presented in this Declaration is based on raw data of HbA1 c%, which are not related to the above corrected errors.

### **Conclusion**

19. It is my opinion that the Experiments described above demonstrating the use of pioglitazone hydrochloride in combination with sibutramine, clearly show unexpected results.

20. I, the undersigned, declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 27 day of March, 2008.



Hiroyuki ODAKA